

The safety of intranasal steroids during pregnancy: A good start



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Approximately 20% of women of childbearing age have allergic diseases, and substantial nasal symptoms occur in approximately 30% of pregnant women.¹ The most common causes of nasal symptoms during pregnancy are allergic rhinitis, sinusitis, and pregnancy rhinitis.² Allergic rhinitis is usually pre-existing, although it can develop or be recognized for the first time during pregnancy.

The treatment of allergic rhinitis during pregnancy is not very different from that of the nonpregnant woman. The mainstays of therapy for allergic rhinitis in pregnant patients are avoidance of triggers, oral antihistamines, and intranasal glucocorticoids. Previous US Food and Drug Administration (FDA) labeling designated budesonide a Category B drug. In the case of budesonide, this meant that even though animal studies demonstrated teratogenicity, adequate human data (from studies of inhaled but not intranasal budesonide) suggested safety. As a result, some clinicians choose budesonide if starting intranasal glucocorticoids for the first time during pregnancy, although no important differences in efficacy or safety have been demonstrated between the various intranasal glucocorticoid preparations. Not until this issue's article from Berard et al³ has there been a human study aimed specifically at determining the safety of intranasal corticosteroid use during pregnancy.

This population-based prospective cohort study identified intranasal triamcinolone-exposed, other intranasal corticosteroid-exposed, and nonexposed women. Using prescription claims records, the authors found no significant relationships between receipt of intranasal triamcinolone and increased risks of overall congenital malformations, most groups of specific malformations, spontaneous abortions, or being small for gestational age. The authors did find that intranasal triamcinolone dispensing was associated with an increased risk of respiratory defects (odds ratio, 2.71; 95% CI, 1.11-6.64; 50 exposed cases).

The strengths and limitations of the study are generally well discussed by the authors. One of the main strengths of this study is the assembly of its large pregnancy cohort from well-validated

databases. Although its size is an advantage, confounding factors might still affect outcomes. The authors adjusted for confounders, such as socioeconomic status, and comorbidities, such as asthma and hypertension. Confounding by indication was also reduced because other intranasal corticosteroid prescriptions were captured and not associated with any of the outcomes. However, one limitation is that there was missing information on other potential confounders, such as smoking, alcohol use, and over-the-counter antihistamine and decongestant exposure.

The data from the unique study of Berard et al³ are generally reassuring regarding exposure to intranasal corticosteroids and important perinatal outcomes. Notably, previously demonstrated relationships between corticosteroids and oral clefts were not confirmed in this study. However, the authors report that intranasal triamcinolone use was associated with an increased risk (adjusted odds ratio, 2.71; 95% CI, 1.11-6.64) of respiratory system defects, as listed in Table E2.

What can we make of that association? It is unlikely to be due to confounding by indication, as mentioned above and by the authors. Although it could be due to the unmeasured confounders described above, this explanation seems unlikely because it would require an imbalance in these unmeasured confounders between triamcinolone recipients and women who received other intranasal corticosteroids. The association could represent a cause-and-effect relationship, with the biologic plausibility described by the authors, but this will certainly require independent confirmation. A very possible explanation is chance because a *P* value of less than .05 suggests that 1 in 20 significant associations can be found by chance, and there are 20 comparisons in Table II alone.

Although asthma during pregnancy has been associated with an increased risk of adverse perinatal outcomes for both mother and baby,⁴ which was confirmed in the current study regarding spontaneous abortion, overall congenital malformations, and being small for gestational age, allergic rhinitis during pregnancy appears to be more benign. However, uncontrolled allergic rhinitis can lead to increased snoring, which has been found to be associated with an increased risk of gestational hypertension (odds ratio, 2.36; 95% CI, 1.48-3.77) during pregnancy.⁵ Although this was not an outcome evaluated by the authors of the current article, this is a potential complication that should be recognized by clinicians caring for pregnant patients with rhinitis.

The authors make several references to the previous FDA pregnancy categories, which were first established in 1979. However, it is important to note that a new FDA labeling format became effective in June 2015. The previous category system was believed to be overly simplistic and at times misleading. The new FDA labeling requirements provide a more complete statement of the known risks based on the available animal and human data, as well as a discussion of benefit/risk considerations. The letter

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categories for all prescription drugs are to be removed over the next 3 to 5 years and replaced by data, such as those from the current study.

Finally, what are the clinical implications of this important study? Overall, we believe it supports the use of intranasal corticosteroids when indicated during pregnancy. Pending further studies, one might want to choose intranasal fluticasone or mometasone for first-trimester use because no adverse associations were found with these intranasal corticosteroids along with higher first-trimester exposure than triamcinolone in the current study. Specifically, 912 women had first-trimester exposure to fluticasone and 1127 had first-trimester exposure to mometasone compared with 318 for triamcinolone.

Because pregnant women are generally excluded from clinical trials, there is a general lack of adequate prospective safety information for most medications taken during pregnancy. Moreover, large-scale randomized controlled trials to determine drug safety during pregnancy are usually not considered ethical. More large, valid, observational studies with relevant comparison

groups, such as the study of Berard et al,³ are needed so that clinicians can prescribe therapy with the best balance of benefits and risks for their pregnant patients.

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